

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 April 2003 (17.04.2003)

PCT

(10) International Publication Number
WO 03/030881 A1

(51) International Patent Classification⁷: A61K 9/70, 9/00, 47/36

(21) International Application Number: PCT/US02/32542

(22) International Filing Date: 11 October 2002 (11.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/328,868 12 October 2001 (12.10.2001) US
10/074,272 14 February 2002 (14.02.2002) US
60/371,940 11 April 2002 (11.04.2002) US
60/386,937 7 June 2002 (07.06.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- of inventorship (Rule 4.17(iv)) for US only
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/030881 A1

(54) Title: GLUCAN BASED FILM DELIVERY SYSTEMS

(57) Abstract: An ingestible water-soluble delivery system in the form of a film composition comprising a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5. Delivery system films of the present invention include a low content of pullulan and can include a relatively high content of a pharmaceutical, cosmetic, or biologically-active agent.

GLUCAN BASED FILM DELIVERY SYSTEMS

5 FIELD OF THE INVENTION

The invention relates to film delivery systems, especially suitable for oral delivery, which can be formed during manufacture in the form of large film strips or sheets and subsequently cut into uniform dosage units, each dosage unit being uniform in content and having distributed therein a glucan, such as pullulan, a water-soluble polymer and optionally 10 an active component.

BACKGROUND OF RELATED TECHNOLOGY

Self-supporting glucan films, such as those made from pullulan and elsinan, are known as being useful for the delivery of edible or ingestible components, for packaging and 15 wrapping as well as other uses. For example, U.S. Patent No. 4,562,020 to Haijiya, et al. discloses a continuous process for producing such self-supporting glucan films formed from aqueous glucan solutions whereby the solution is deposited on a corona-treated plastic conveyor belt and air dried to form thin films. A variety of additional ingredients, such as 20 flavors, colors, seasonings, cyclodextrine, protein, fat, vitamin, hormones, anti-genic substances, antibiotics, biologically active substances, viruses, lecithin, plasticizers, micro-organisms, spores, seeds and the like are disclosed as being useful additives.

Pullulan is a desirable material for forming edible films because of its high water solubility, rapid dissolution and excellent mouth-feel. However, due to its relatively low 25 molecular weight as compared to many polymeric film forming materials, it is difficult to achieve films having low pullulan content. This is because, due to the low viscosity of pullulan, high amounts of pullulan must be present in the aqueous solution for good film casting. Generally, the pullulan content must be greater than 20% by weight in order to form 30 a useful film. When insoluble additives are to be added to such pullulan solutions, even more pullulan must be used in order to achieve sufficient viscosity to prevent separation of the insoluble particulate from the solution prior to or during the film forming process. For example, many useful pharmaceutical and cosmetic active agents are water insoluble particulates. These particulates must be uniformly dispersed throughout the pullulan solution and must remain uniformly dispersed in the film forming process, such that the resultant

films have uniform drug content. For example, by uniform content it is meant that unit dosages cut from larger pieces of film will not substantially vary in the amount of drug content. In particular, the drug content of any one unit dosage should not vary more than 10% in order to be acceptable for sale under regulations by the U.S. Federal Drug

5 Administration (FDA) or other world regulatory authorities regulations.

Films made from pullulan to-date also suffer the limitation that in order to put higher drug levels in the film, increased pullulan content is necessary in order to achieve uniformity in film content.

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U.S. Patent No. 4,927,636 to Haijiya, et al. discloses pullulan films which have decreased solubility in water. These films are made from a combination of pullulan and polyethylene glycol (PEG) which form an “association complex” to produce this effect. Polyethylene glycols within the molecular range of 400 to 10,000 are disclosed as useful.

15 The ratio of pullulan to PEG is disclosed as being 1 part by weight (pbw) pullulan to 0.01 to 100 part by weight (pbw) PEG. This patent discloses that pullulan in combination with other water-soluble polymers does not form such an association complex useful for decreasing solubility and reducing adhesive and stickiness properties of aqueous pullulan.

20 U.S. Patent No. 5,411,945 to Ozaki, et al. discloses a pullulan binder composition made from a combination of pullulan and a mono-saccharide or lower molecular weight oligo-saccharide in a ratio of 85:15 to 65:35 pullulan/saccharide. These films are disclosed as being gradually dissolvable.

25 U.S. Patent No. 5,518,902 to Ozaki, et al. discloses high pullulan content products made by cultivating micro-organisms capable of producing pullulan at a pH exceeding 2.0 but not higher than 4.0 in a nutrient culture medium containing 10-20 w/v % of a polysaccharide to produce pullulan, while controlling the viscosity of the nutrient culture to below 30 cps.

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U.S. Patent Application Publication No. 2001/0022964 A1 to Leung, et al. discloses edible films made from pullulan and which include anti-microbial effective amounts of essential oils. A variety of polymers may be used as film formers in addition to pullulan.

Various drugs may be included in the films. The content of pullulan used is very high and the drug loading is very low, as is typical of pullulan films.

It would be desirable to have film products made from pullulan which can include 5 high content active ingredients, such as pharmaceutical and/or cosmetic agents, and which have relatively low pullulan content. It would also be advantageous to provide water-soluble, edible films which have uniformity of active content, both in the manufacturing scale and in the unit dosage, final product form.

10 SUMMARY OF THE INVENTION

The present invention seeks to attain low content, high pharmaceutical and/or cosmetic active content films which have enhanced flexibility, structural integrity and uniformity. The present invention also provides for a unique method of producing the inventive compositions such that uniform distribution of the compositional components are 15 evenly distributed throughout the film. This process is described in detail in co-pending U.S. Patent Application No. 10/074,272, entitled "Thin Film with Non-Self-Aggregating Uniform Heterogeneity and Drug Delivery Systems Made Therefrom", the subject matter of which is herein incorporated by its entirety.

20 In one aspect of the present invention there is included an edible water-soluble delivery system in the form of a film composition which includes a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5. Desirably, a pharmaceutical and/or cosmetic active components is present in the delivery system in amounts effective for its intended use, desirably, due to the advantages of 25 the aforementioned glucan/water-soluble polymer ratio, high amounts of active components may be present without disrupting the uniformity of content of the overall film and subsequently the individual dosage forms cut therefrom. Significantly lower amounts of pullulan, as compared to conventional pullulan films, can be used while maintaining a high load of active components. Increased flexibility as compared to pullulan or the water-soluble 30 polymers being used along is achieved, as well as enhanced tensile strength and overall structural integrity. Elongation of the resultant film is substantially unaffected as compared to pullulan alone.

In another aspect of the present invention there is included a pharmaceutical composition in the form of a film for enteral or topical administration, which includes a composition having a uniformly distributed combination of a glucan, a water-soluble polymer, a polar solvent, and a pharmaceutical active, wherein said glucan and said water-soluble polymer are present in a ratio of about 40:1 to about 0.1:5, said composition in its dried film form maintaining the uniform distribution of components through the application of controlled bottom drying of the film.

In another aspect of the present invention there is included a pharmaceutical and/or cosmetic dosage form which includes a film having a uniformly dispersed composition including a glucan and a water-soluble polymer, a pharmaceutical and/or cosmetic active and a solvent, said film being formed by depositing a wet film of said composition onto a substrate surface and controllably drying the wet film from the side contacting the substrate to prevent self-aggregation and achieve compositional uniformity.

In a further aspect of the present invention there is provided a pharmaceutical and/or cosmetic dosage form including an edible water-soluble film composition which includes a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5 having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a side view of a package containing a unit dosage film of the present invention.

Figure 2 shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

Figure 3 shows a side view of the adjacently coupled packages of Figure 2 arranged in a stacked configuration.

Figure 4 shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

Figure 5 is a schematic view of a roll of coupled unit dose packages of the present invention.

5 Figure 6 is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

10 Figure 7 is a schematic view of an apparatus suitable for drying the films of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

15 Glucans useful in the present invention include pullulan and elsinan. These materials substantially contain repeating maltotriose units and are produced by culturing a strain of species *Aureobasidium pullulans* or genus *Elsino* on a nutrient medium containing sugars under aeration and agitation conditions. The cellular debris is removed and the resultant supernatant is purified and filtrated to yield the resultant glucan. The molecular weight of the glucan may vary widely, but generally are commercially available at molecular weights of 50,000 to 100,000. Due to the relatively low molecular weight, water solubility is very high and attaining useful viscosities for film forming requires a high content of pullulan;

20 Water-soluble polymers useful in the present invention cellulosic materials, gums, proteins, starches, and combinations thereof.

25 Examples of cellulosic materials include, without limitation, carboxymethyl cellulose, hydroxyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose hydroxypropylmethyl cellulose, and combinations thereof.

30 Examples of water-soluble gums include gum arabic, xanthan gum, tragacanth, acacia, carageenan, guar gum, locust bean gum, pectin, alginates and combinations thereof.

35 Examples of other polymeric materials include polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, poly(meth)acrylate, poly(meth)copolymers and combinations thereof.

Useful starches include gelatinized, modified or unmodified starches. The source of the starches may vary and include tapioca, rice, corn, potato, wheat and combinations thereof.

Useful water-soluble protein polymers gelatin, zein, gluten, soy protein, soy protein isolate, whey protein, whey protein isolate, casein, levin, collagen and combinations thereof. Additional water-soluble polymers include dextrin, dextran and combinations thereof, as well as chitin, chitosin or combinations thereof, and polydextrose.

To achieve the desired results of the present invention of film content uniformity, the ratio of glucan to water-soluble polymer is about 40:1 to 0.1:5, desirable about 20:1 to 0.5:5 and more desirably 10:1 to about 1:5.

The ingestible water-soluble delivery system of the present invention further include an active component selected from cosmetic agents, pharmaceutical agents, bioactive agents and combinations thereof. The active component may be present in any amount effective for the intended treatment. It is particularly desirable and an advantage of the present invention that the active component can be included in high loads. For example, the active component may be present in amounts up to about 60% by weight of the total composition and desirably in amounts of 0.01% to about 50% by weight of total composition.

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The edible water-soluble delivery system of the present invention further includes one or more members selected from taste-masking agents, plasticizing agents, surfactants, emulsifying agents, thickening agents, binding agents, cooling agents, saliva-stimulating agents, sweetening agents, antimicrobial agents and combinations thereof.

25

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal,

ophthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by 5 preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is 10 ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is 15 desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will 20 adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' 25 tendency to dissolve quickly when introduced to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture 30 resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to Figure 1, a packaged pharmaceutical dosage unit 10, includes each film 12 individually wrapped in a pouch or between foil and/or plastic laminate sheets 14. As depicted in Figure 2, the pouches 10, 10' can be linked together with tearable or perforated joints 16. The pouches 10, 10' may be packaged in a roll as depicted in Figure 5 or stacked as shown in Figure 3 and sold in a dispenser 18 as shown in

Figure 4. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

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Rheology and Films Properties

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Patent No. 4,631,837 to

Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

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The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside 10 subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top 15 air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would 20 cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted 25 to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity 30 to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the 5 bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the 10 particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder 15 or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable 20 film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_l) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (V_o) of a rigid spherical body of radius (r) in a viscous fluid, as 25 follows:

$$V_o = (2gr^2)(\rho_p - \rho_l)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids 30 volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of

particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v , can be expressed as:

$$v/V_o = 1/(1 + \kappa\phi)$$

where κ = a constant, and ϕ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o = 1 + 2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o = 1 + 2.5\phi + C_1\phi^2 + C_2\phi^3 + \dots$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., $<500\mu\text{m}$. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{\max} = 3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

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A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt%, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of $10 - 10^5 \text{ sec.}^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)} = \alpha_0^{(n-1/n)} - ((n-1)/(2n-1))(\tau/K)^{1/n} (2\pi/\lambda)^{(3+n)/n} h^{(2n+1)/n} t$$

where α is the surface wave amplitude, α_0 is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart

or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote 5 thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the 10 present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to 15 maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or 20 other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is 25 one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps ("cps" or "centipoise") to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

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The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be

adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or 5 stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

10 **Film Component Mixing:**

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation 15 of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to 20 casting. Thus, the masterbatch pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. 25 For example, the ingredients may all be added together or a pre-mix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

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Figure 6 shows an apparatus 20 suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch 22, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank 24. The components for pre-mix or master batch

22 are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank 24. Then a pre-determined amount of the master batch is controllably fed via a first metering pump 26 and control valve 28 to either or both of the first and second mixers, 30, 30'. The present invention, however, is not limited to the use of two mixers, 30, 30', and any 5 number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers 30, 30', such as parallel sequencing as depicted in Figure 6, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, 32, 32', in each of the mixers, 10 30, 30'. Desirably, the residence time of the pre-mix or master batch 22 is minimized in the mixers 30, 30'. While complete dispersion of the drug into the pre-mix or master batch 22 is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers 30, 30' are often smaller, i.e. lower 15 residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch 22. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan 36 through the second metering pumps, 34, 34'. The metering roller 38 determines the thickness of the film 42 and applies it to the application roller. The film 42 is finally formed on the substrate 44 and carried away via the support roller 46.

20

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into 25 a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

30

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in

other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

5 Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

10 Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

15 The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

20 Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

25 In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

30 In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

5 In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed "Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

10 The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap" between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

15 Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

20 In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

25 While the proper viscosity, uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this 30 method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of

heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

5 Desirably, the film is dried from the bottom of the film to the top of the film. Substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first ½ minute to about the first 4 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's 10 top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying 15 means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

20 The temperature at which the films are dried is about 100°C or less, desirably about 90°C or less, and most desirably about 80°C or less.

25 Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

30 A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared

radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate 5 through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

10 The films may initially have a thickness of about 500 μm to about 1,500 μm , or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm , or about 0.1mils to about 10mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

15 The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film 48 as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates 20 drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a 25 condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow 30 is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot

break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities 5 may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, which may have a low 10 degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. 15 Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be 20 added to the film 42 prior to the drying of the film 42. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the 25 film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securely disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully 30 embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and

sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus 50 is depicted in Figure 7. Drying apparatus 50 is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film 42 which is disposed on substrate 44. Hot air enters the entrance end 52 of the drying apparatus and travels vertically upward, as depicted by vectors 54, towards air deflector 56. The air deflector 56 redirects the air movement to minimize upward force on the film 42. As depicted in Figure 7, the air is tangentially directed, as indicated by vectors 60 and 60', as the air passes by air deflector 56 and enters and travels through chamber portions 58 and 58' of the drying apparatus 50. With the hot air flow being substantially tangential to the film 42, lifting of the film as it is being dried is thereby minimized. While the air deflector 56 is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends 62 and 62' of the drying apparatus 50 are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors 64 and 64', which tend to provide a pulling or drag effect of the film 42 to prevent lifting of the film 42. Lifting of the film 42 may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film 42 as the film 42 and/or substrate 44 lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the

film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a polar organic solvent including, 5 but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

It has also been unexpectedly discovered that high temperature fat materials, e.g. M.P. 55°C or greater, can be used to encapsulate dry particles before or after enteric coating. The 10 drying process temperatures are sufficiently rapid and low, and evaporative cooling effect as a result of water vapor loss is sufficiently high enough, that the fat does not appreciably melt.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact 15 material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than 20 a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

Uses of Thin Films

25 The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate 30 that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, ophthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed 5 prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives 10 themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back 15 of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

20 Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduced to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

25 The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to Figure 1, a packaged pharmaceutical dosage unit 10, includes each film 12 individually wrapped in a pouch or between foil and/or 30 plastic laminate sheets 14. As depicted in Figure 2, the pouches 10, 10' can be linked together with tearable or perforated joints 16. The pouches 10, 10' may be packaged in a roll as depicted in Figure 5 or stacked as shown in Figure 3 and sold in a dispenser 18 as shown in Figure 4. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more

convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

5 Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

Rheology and Films Properties

10 For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a
15 high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat
20 drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity
25 of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform
30 heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Patent No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the

films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that

5 avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by

10 drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet

15 alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be

20 controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

25 This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of

30 the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the

introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

5 The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method 10 of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

15 In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the 20 present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_l) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (V_o) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o = (2gr^2)(\rho_p - \rho_l)/9\mu$$

25 At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

30 Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v , can be expressed as:

$$v/V_o = 1/(1 + \kappa\phi)$$

where κ = a constant, and ϕ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

5 Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o = 1 + 2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At 10 higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o = 1 + 2.5\phi + C_1\phi^2 + C_2\phi^3 + \dots$$

where C is a constant.

15 The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed 20 phase.

25 The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., $<500\mu\text{m}$. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear 30 stress developed in settling through a medium of given viscosity can be given as

$$\tau_{\max} = 3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to 5 lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent 10 shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. 15 This is due to the need to produce a stable suspension of particles, for example 30-60 wt%, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of $10 - 10^5 \text{ sec.}^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

20 In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)} = \alpha_0^{(n-1/n)} - ((n-1)/(2n-1))(\tau/K)^{1/n} (2\pi/\lambda)^{(3+n)/n} h^{(2n+1)/n} t$$

25 where α is the surface wave amplitude, α_0 is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a 30 very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic

fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As 5 described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially 10 spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

15 Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

20 The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps ("cps" or "centipoise") to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and 25 most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

30 The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or

by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

Film Component Mixing:

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air 10 bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-15 forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

20 When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a pre-mix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially 25 important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

Figure 6 shows an apparatus 20 suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch 22, which 30 includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank 24. The components for pre-mix or master batch 22 are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank 24. Then a pre-determined amount of the master batch is controllably fed via a first metering pump 26 and control valve 28 to either or both of the first and second mixers, 30,

30'. The present invention, however, is not limited to the use of two mixers, 30, 30', and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers 30, 30', such as parallel sequencing as depicted in Figure 6, and other sequencing or arrangements of mixers, such as series or combination of parallel 5 and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, 32, 32', in each of the mixers, 30, 30'. Desirably, the residence time of the pre-mix or master batch 22 is minimized in the mixers 30, 30'. While complete dispersion of the drug into the pre-mix or master batch 22 is desirable, excessive residence times may result in leaching or dissolving of the drug, 10 especially in the case for a soluble drug. Thus, the mixers 30, 30' are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch 22. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan 36 through the second metering pumps, 34, 34'. The metering roller 38 15 determines the thickness of the film 42 and applies it to the application roller. The film 42 is finally formed on the substrate 44 and carried away via the support roller 46.

Forming the Film

20 The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be 25 accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

30 Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion 5 coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent 10 control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

15

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

20

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath 25 of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known 30 as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed

“Extrusion” and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

5 The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a “gap” between a “knife” and a support roller. As the coating and substrate pass through, the excess is scraped off.

10 Air knife coating is where the coating is applied to the substrate and the excess is “blown off” by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

15 In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

20 While the proper viscosity, uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate.

25 An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

30 When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film.

Substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first

5 few minutes, e.g. about the first ½ minute to about the first 4 minutes of the drying process.

Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides.

Then, heat is initially applied to the bottom side of the film to provide the necessary energy to 10 evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

15

The temperature at which the films are dried is about 100°C or less, desirably about 90°C or less, and most desirably about 80°C or less.

Another method of controlling the drying process, which may be used alone or in 20 combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

A specific example of an appropriate drying method is that disclosed by Magoon.

25 Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its 30 surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this

creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the
5 film.

The films may initially have a thickness of about 500 μm to about 1,500 μm , or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm , or about 0.1 mils to about 10 mils. Desirably, the dried films will have a thickness of about 2
10 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film 48 as described herein. Controlled bottom drying or controlled microwave drying
15 advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath
20 are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and
25 bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical
30 aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions,

low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

5 Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as 10 compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

15 Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film 42 prior to the drying of the film 42. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface 20 of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being 25 embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

30 The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus 50 is depicted in Figure 7. Drying apparatus 50 is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film 42 which is disposed on substrate 44. Hot air enters the entrance end 52 of the drying apparatus and travels vertically upward, as depicted by vectors 54, towards air deflector 56. The air deflector 56 redirects the air movement to minimize upward force on the film 42. As depicted in Figure 7, the air is tangentially directed, as indicated by vectors 60 and 60', as the air passes by air deflector 56 and enters and travels through chamber portions 58 and 58' of the drying apparatus 50. With the hot air flow being substantially tangential to the film 42, lifting of the film as it is being dried is thereby minimized. While the air deflector 56 is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends 62 and 62' of the drying apparatus 50 are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors 64 and 64', which tend to provide a pulling or drag effect of the film 42 to prevent lifting of the film 42. Lifting of the film 42 may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film 42 as the film 42 and/or substrate 44 lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most

desirably less than about 2%. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

5 It has also been unexpectedly discovered that high temperature fat materials, e.g. M.P. 55°C or greater, can be used to encapsulate dry particles before or after enteric coating. The drying process temperatures are sufficiently rapid and low, and evaporative cooling effect as a result of water vapor loss is sufficiently high enough, that the fat does not appreciably melt.

10 Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no 15 more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

20 The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

25 EXAMPLES

Examples 1-8:

A variety of films were produced using the aforementioned inventive ratios of pullulan to water-soluble polymer. As an insoluble active component, calcium carbonate was used.

30 The compositions in Table 1 below were made in accordance with the process set forth in co-pending U.S. Application No. 10/074,272. The resultant uncut film exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of $\frac{3}{4}$ " by 1" by 5 mils cut therefrom.

TABLE 1

| Films Containing Pullulan/Water-Soluble Polymer Combinations With Insoluble Calcium Carbonate Active | | | | |
|--|---------------------|----------------|----------------|----------------|
| Components | Grams (% by weight) | | | |
| | 1 | 2 | 3 | 4 |
| Pullulan ¹ | 5.0 (15.5) | 10.0 (23.5) | 20.0 (42.1) | 15.0 (35.2) |
| Modified Cellulose | 3.0 (9.3) | -- | -- | -- |
| Starches | -- | 10.0 (23.5) | -- | -- |
| Carageenan Gum | -- | -- | 4.0 (8.4) | -- |
| Xantham Gum | -- | -- | -- | 3.0 (7.0) |
| Alginate | -- | -- | -- | -- |
| Polyvinyl-pyrrolidone | -- | -- | -- | -- |
| Loratadine | -- | -- | -- | -- |
| Calcium Carbonate | 10.0 (31.0) | 10.0 (23.5) | 10.0 (21.1) | 10.0 (23.5) |
| Mint Flavor | 2.5 (7.7) | 2.0 (4.7) | 2.0 (4.2) | 2.5 (5.9) |
| Artificial Sweeteners | 2.0 (6.2) | 1.5 (3.5) | 1.5 (3.2) | 2.0 (4.7) |
| Tween 80 | 3.0 (9.3) | 2.5 (5.9) | 2.5 (5.3) | 2.5 (5.9) |
| Antifoaming agent | 0.2 (0.6) | 0.2 (0.5) | 0.2 (0.4) | 0.2 (0.5) |
| Propylene Glycol | 4.0 (12.4) | 3.0 (7.0) | 3.5 (7.4) | 4.0 (9.4) |
| Water ¹ , Potable | 180 (8.0) | 80 (8.0) | 100 (8.0) | 120 (8.0) |

¹ The dried film was assumed to have a moisture content of about 6.0-8.0% by weight.

² Other non-limiting Gums/Food Polymers may be used in combination with Pullulan: Pectin, Carboxymethyl Cellulose, Hydroxypropyl Cellulose, Polyvinyl Alcohol, Gum Arabic, Polyacrylic Acid, Dextrim, Gelatin, Zein, Soy Protein Isolate, Whey Protein Isolate, Milk Casein and combinations thereof.

TABLE 1 cont'd

| Films Containing Pullulan/Water-Soluble Polymer Combinations With Insoluble Calcium Carbonate Active | | | | |
|---|----------------------------|----------------|----------------|----------------|
| Components | Grams (% by weight) | | | |
| | 5 | 6 | 7 | 8 |
| Pullulan ¹ | 25.0 (39.1) | 30.0 (8.7) | 20.0 (43.6) | 0.4 (1.6) |
| Modified Cellulose | -- | -- | 2.0 (4.4) | 2.0 (8.0) |
| Starches | -- | -- | -- | -- |
| Carageenan Gum | -- | -- | -- | -- |
| Xantham Gum | -- | -- | -- | -- |
| Alginate | 3.0 (4.6) | -- | -- | -- |
| Polyvinyl-pyrrolidone | -- | 8.0 (2.3) | -- | -- |
| Loratadine | \-- | -- | 10.0 (21.8) | 12.0 (47.8) |
| Calcium Carbonate | 10.0 (15.4) | 10.0 (12.5) | -- | -- |
| Mint Flavor | 2.5 (3.9) | 2.0 (3.1) | 2.0 (4.4) | 1.5 (6.0) |
| Artificial Sweeteners | 2.0 (3.1) | 2.0 (3.1) | 2.0 (4.4) | 1.5 (6.0) |
| Tween 80 | 3.0 (4.6) | 2.5 (3.9) | 2.0 (4.4) | 1.5 (6.0) |
| Antifoaming agent | 0.2 (0.3) | 0.2 (0.3) | 0.2 (0.4) | 0.2 (0.8) |
| Propylene Glycol | 4.0 (6.2) | 4.0 (6.2) | 4.0 (8.7) | 4.0 (15.9) |
| Water ¹ , Potable | 140 (8.0) | 100 (8.0) | 150 (8.0) | 120 (8.0) |

¹ The dried film was assumed to have a moisture content of about 6.0-8.0% by weight.

² Other non-limiting Gums/Food Polymers may be used in combination with Pullulan: Pectin, Carboxymethyl Cellulose, Hydroxypropyl Cellulose, Polyvinyl Alcohol, Gum Arabic, Polyacrylic Acid, Dextrim, Gelatin, Zein, Soy Protein Isolate, Whey Protein Isolate, Milk Casein and combinations thereof.

Examples 9-11:

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated castor oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be

essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-forming 5 compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

10

TABLE 2

| Ingredient | (parts by wt.) 9 |
|------------------------------------|---------------------|
| POLYMERS: | |
| Hydroxypropylmethyl cellulose | 15.6 |
| Cornstarch ¹ | 10.41 |
| Polyvinylpyrrolidone | 10.41 |
| Xanthan Gum | 1.14 |
| SURFACTANT²: | 2.0 |
| PLASTICIZER³: | 11.67 |
| ANTI-FOAM AGENT⁴ | 2.44 |
| OTHER | |
| Spearmint Flavor | 10.43 |
| Loratadine (drug) | 16.62 |
| Calcium Carbonate | 5.54 |
| Sweetener | 9.36 |

¹ Available from Grain Processing Corporation as Pure Cote B792

² Ethoxylated castor oil, Cremophor® EL available from BASF

³ Propylene Glycol

⁴ Silicone Emulsion

15

20

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 5% moisture remained. The formula coated 5 and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 3

| Ingredient | (parts by wt.) |
|---|-----------------------|
| POLYMERS: | 10 |
| Hydroxypropylmethyl cellulose | 15.6 |
| Cornstarch ¹ | 10.41 |
| Polyvinylpyrrolidone | 10.41 |
| PLASTICIZER/SOLVENT²: | 22.1 |
| ANTI-FOAM AGENT³ | 2.44 |
| OTHER | |
| Raspberry Flavor | 0.3 |
| Calcium Carbonate ⁴ | 30.38 |
| Sweetener | 8.36 |

¹ Available from Grain Processing Corporation as Pure Cote B792

² Propylene Glycol

³ Polydimethyl Siloxane Emulsion

⁴ Functioned to mimic drug loading

10

The above ingredients were added to water at 40% until a homogeneous suspension 15 was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 4

| Ingredient | (parts by wt.) |
|------------------------------------|-----------------------|
| POLYMERS: | 11 |
| Hydroxypropylmethyl cellulose | 7.8 |
| Hydroxypropyl cellulose | 7.8 |
| ANTI-FOAM AGENT¹ | 0.75 |
| OTHER | |
| Peppermint & Bittermint Flavor | 2.25 |
| Tastemasking Flavor ² | 0.3 |
| Calcium Carbonate ³ | 15.2 |
| Sweeteners | 0.9 |

¹Polydimethyl Siloxane Emulsion²Prosweet from Virginia Dave³Functioned to mimic drug loading

5

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

10

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The tastemasking flavor is an ingredient that effects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

15

Examples 12-15:

The following examples of the present invention describe film-forming compositions analyzed for uniformity and stability. Film-forming compositions were formed as shown below in Table 5.

20

TABLE 5

| Ingredient | (grams) | | | |
|-------------------------------|----------------|-----------|-----------|-----------|
| | 12 | 13 | 14 | 15 |
| Pullulan | 7.0 | 7.0 | | |
| Hydroxypropylmethyl cellulose | | 7.0 | 7.0 | 10.5 |
| Hydroxypropyl cellulose | | | 7.0 | 3.5 |
| Polydimethylsiloxane emulsion | 0.14 | 0.14 | 0.14 | 0.14 |
| Water | 86 | 86 | 86 | 86 |

The above ingredients were stirred and mixed under vacuum to eliminate entrapped
5 air. Seventy grams of each solution and five grams of glass beads were combined into four
ounce jars and manually shook for about one minute to completely mix the glass beads into
the solutions. The mixed samples were placed aside for ten minutes. After ten minutes a 10
ml sample was obtained from the top surface of each jar by use of a syringe.

10 The 10 ml samples were filtered through a funnel containing filter paper. The
materials collected on the filter were washed with water to leave the glass beads on the paper.
The filter papers with the glass beads were then dried for ten minutes at 90°C. The weight of
the filter and the resulting glass beads were measured, as shown below in Table 6.

15

TABLE 6

| Ingredient | (grams) | | | |
|--|----------------|-----------|-----------|-----------|
| | 12 | 13 | 14 | 15 |
| Weight of filter paper and glass beads collected after drying | 0.332 | 0.509 | 0.839 | 0.831 |
| Initial weight of filter paper | 0.151 | 0.143 | 0.143 | 0.140 |
| Weight of glass beads collected | 0.181 | 0.366 | 0.696 | 0.691 |

Samples 14 and 15 contained considerably more glass beads than sample 12, which
was made from pullulan. This indicated the significant particulate, i.e. glass beads, settling
20 occurred with composition containing only pullulan as the polymer. The viscosity of pullulan
is thus too low to provide a film-forming matrix that can maintain uniformity of particulates
therein. Increasing the amount of other polymers, such as hydroxypropylmethyl cellulose,
significantly increases the film stability and uniformity, as noted by the increased weight of
the glass beads.

25

While there have been described what are presently believed to be the certain desirable embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the
5 invention.

WHAT IS CLAIMED IS:

1. An ingestible water-soluble delivery system in the form of a film composition comprising a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5.
5
2. The ingestible water-soluble delivery system of claim 1, wherein the ratio is about 10:1 to about 1:5.
- 10 3. The ingestible water-soluble delivery system of claim 1, wherein said glucan is selected from the group consisting of pullulan, elsinan and combinations thereof.
4. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is a cellulosic material, a gum, a protein, a starch, and combinations thereof.
15
5. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of carboxymethyl cellulose, hydroxyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose hydroxypropylmethyl cellulose, and combinations thereof.
- 20 6. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of gum arabic, xanthan gum, tragacanth, acacia, carageenan, guar gum, locust bean gum, pectin, alginates and combinations thereof.
- 25 7. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, poly(meth)acrylate, poly(meth)copolymers and combinations thereof.
8. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is a starch selected from the group consisting of tapioca, rice, corn, potato, wheat and combinations thereof.
30
9. The ingestible water-soluble delivery system of claim 8, wherein said starch is gelatinized, modified or unmodified.

10. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is a protein selected from the group consisting of gelatin, zein, gluten, soy protein, soy protein isolate, whey protein, whey protein isolate, casein, levin, collagen and combinations thereof.

5

11. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of dextrin, dextran and combinations thereof.

10 12. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of chitin, chitosin or combinations thereof.

13. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is polydextrose.

15 14. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of dextrin, dextran and combinations thereof.

15. The ingestible water-soluble delivery system of claim 1, further comprising an active component selected from the group consisting of cosmetic agents, pharmaceutical agents, 20 bioactive agents and combinations thereof.

16. The ingestible water-soluble delivery system of claim 1, wherein said active component is present in amounts of up to about 60% by weight of the total composition.

25 17. The ingestible water-soluble delivery system of claim 1, wherein said active component is present in amounts of up to about 0.1% to about 60% by weight of the total composition.

30 18. The ingestible water-soluble delivery system of claim 1, further comprising one or more members selected from the group consisting of taste-masking agents, plasticizing agents, surfactants, emulsifying agents, thickening agents, binding agents, cooling agents, saliva-stimulating agents, sweetening agents, antimicrobial agents and combinations thereof.

19. A dried film formed from the composition of claim 1.

20. A dried film formed from the composition of claim 15.

21. A dried film formed from the composition of claims 1 or 15 having a thickness up to
5 about 5mm.

22. The dried film of claims 19 or 20 having a polymeric carrier backing.

23. The dried film of claims 19 or 20 in unit dosage form sealed in a pouch.

10

24. A pharmaceutical and/or cosmetic dosage form comprising an ingestible water-soluble film composition comprising a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5 having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

15

25. A pharmaceutical and/or cosmetic dosage form comprising a film having a uniformly dispersed composition comprising a glucan and a water-soluble polymer, a pharmaceutical and/or cosmetic active and a solvent, said film being formed by depositing a wet film of said composition onto a substrate surface and controllably drying the wet film from the side
20 contacting the substrate to prevent self-aggregation and achieve compositional uniformity.

26. A pharmaceutical composition in the form of a film for enteral or topical administration, comprising a composition having a uniformly distributed combination of a glucan, a water-soluble polymer, a polar solvent, and a pharmaceutical active, wherein said glucan and said water-soluble polymer are present in a ratio of about 40:1 to about 0.1:5, said composition in its dried film form maintaining the uniform distribution of components through the application of controlled bottom drying of the film.

27. The ingestible water-soluble delivery system of claim 15, wherein said
30 pharmaceutical active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H₂ antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-

parkinsonism drugs, narcotics, analgesics, anti-pyretics, psychopharmacological drugs and combinations thereof.

28. The ingestible water-soluble delivery system of claim 1, wherein the film composition
5 is essentially free of a surfactant.

29. The ingestible water-soluble delivery system of claims 1 or 28, wherein the film composition is essentially free of a plasticizer.

10 30. The ingestible water-soluble delivery system of claims 1, 28 or 29, wherein the film composition is essentially free of a polyalcohol.

31. The pharmaceutical and/or cosmetic dosage form of claims 24 or 25, wherein the film is essentially free of a surfactant.
15

32. The pharmaceutical and/or cosmetic dosage form of claims 24, 25, or 31, wherein the film is essentially free of a plasticizer.

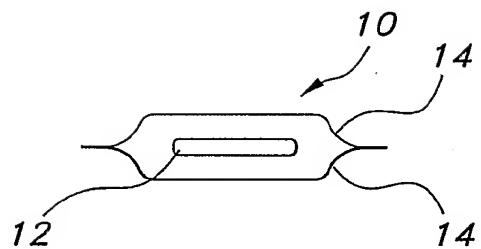
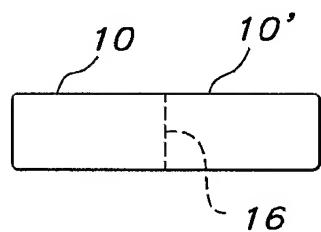
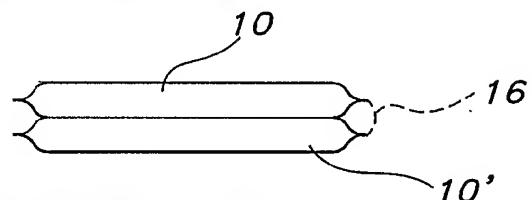
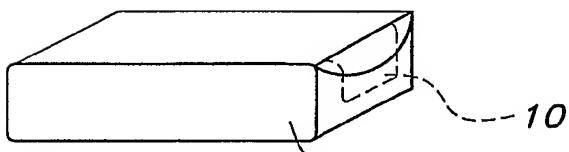
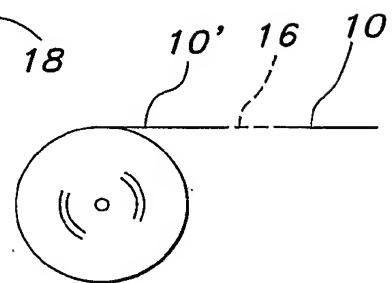
33. The pharmaceutical and/or cosmetic dosage form of claims 24, 25, 31 or 32, wherein
20 the film is essentially free of a polyalcohol.

34. The pharmaceutical composition of claim 26, wherein the film is essentially free of a surfactant.
25

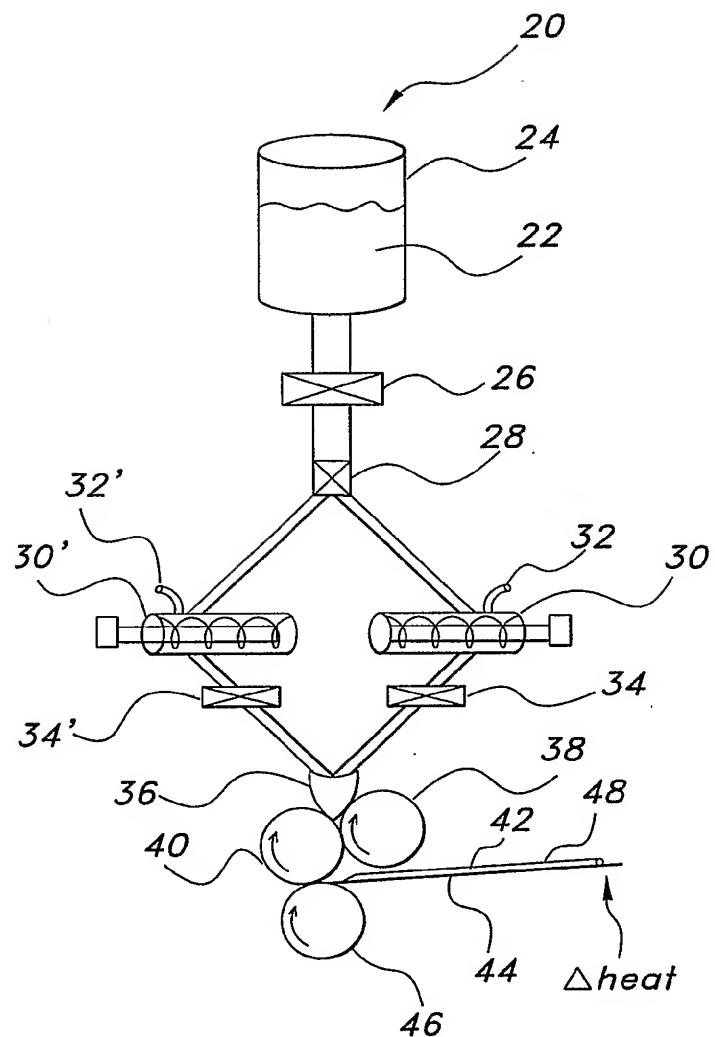
35. The pharmaceutical composition of claims 26 or 34, wherein the film is essentially free of a plasticizer.

36. The pharmaceutical composition of claims 26, 34 or 35, wherein the film is essentially free of a polyalcohol.
30

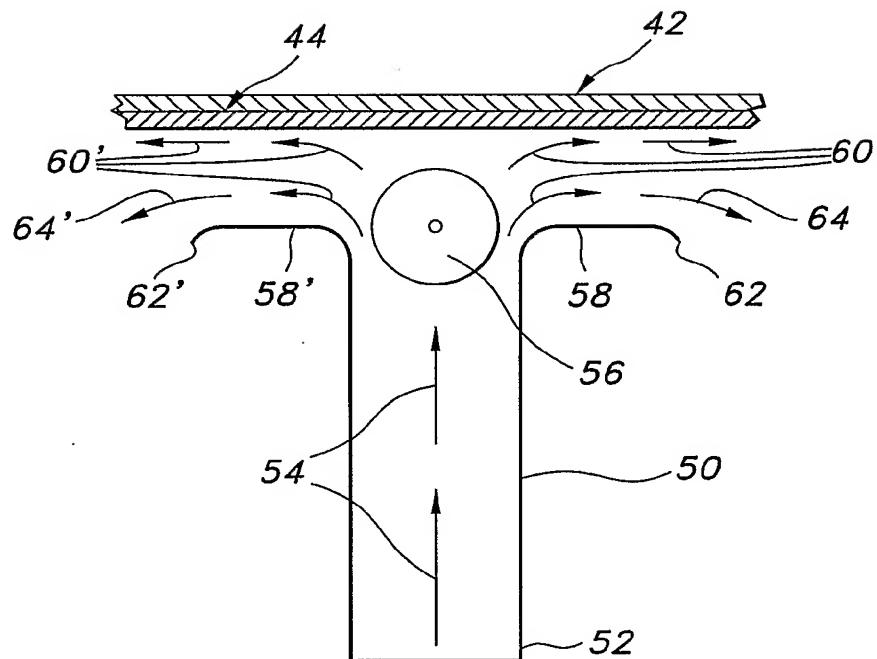
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**FIG 1****FIG 2****FIG 3****FIG 4****FIG 5**

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**FIG. 6**

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**FIG. 7**

INTERNATIONAL SEARCH REPORT

PCT/US 02/32542

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K9/70 A61K9/00 A61K47/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, FSTA, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| | | -/- |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

30 January 2003

06/02/2003

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INTERNATIONAL SEARCH REPORT

PCT/US 02/32542

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
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| X | WO 01 70194 A (WARNER LAMBERT CO) 27 September 2001 (2001-09-27) claims; tables --- | 1-36 |
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INTERNATIONAL SEARCH REPORT

PCT/US 02/32542

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1, 19, 24–26 (in part) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 19, 24-26 (in part)

Present claims 1, 24-26, by using the functional definition "water-soluble polymer", relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the delivery systems where the water-souble polymer is as listed in claims 4-14.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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PCT/US 02/32542

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Information on patent family members

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